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Title: Microcalcification-associated breast cancer: HER2-enriched molecular subtype is associated with mammographic features

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Microcalcification-associated breast cancer: HER2-enriched molecular subtype is associated with mammographic features

Purpose: To investigate whether the mammographic features were different between breast cancer HER2-enriched molecular subtype and non-HER2-enriched molecular subtype. **Materials and Methods:** 283 microcalcification-associated breast cancers were identified (HER2-enriched: n=57; non-HER2-enriched: n=226). Mammographic tumor mass and calcification features in relation to HER2 molecular subtype were analyzed. **Results:** On univariate analysis, HER2-enriched molecular subtype rates were significantly higher (a) in tumor size<=2cm 33 of 57 [57.9%]) than in tumor size>2cm lesions (22 of 226 [9.7%]) (*P*=0.007), (b) in non-spiculated mass 39 of 57 [68.4%]) than in spiculated mass lesions (18 of 226 [7.9%]) (P =0.034), (c) in calcifications extent >2 cm (41of 57[71.9%]) lesions than in calcifications extent<=2 cm lesions (16 of 226 [7.1%]) (*P*<0.001)and (d) in calcification density ＞20/cm^2 (44 of 57[71.2%]) lesions than in calcification density<=20/cm^2 lesions (13 of 226 [5.8%]) (*P*=0.034).On multivariate analysis, three mammographic features (tumor size>2cm vs. size⩽2 cm OR: 0.415 95% CI: 0.215 to 0.802, *P*=0.009, spiculated mass vs. non-spiculated mass OR: 0.226 95% CI: 0.114 to 0.446, *P*<0.001 and calcifications extent >2 cm vs. calcifications extent <=2 cm OR: 7.754, 95% CI: 3.100 to 19.339 *P*<0.001) were independent predictors. Our results indicated that small tumor size, non-spiculated mass and calcification extent >2 cm are more likely to be HER2 molecular subtype. The discrimination of this model, as quantified by the AUC, was 0.751 (95%CI: 0.701 to 0.854).**Conclusion:** Our study presents a prediction model that incorporates the mammographic features of tumor size, non-spiculated mass and calcification extent, which can potentially be used to preoperative predict breast cancer HER2-enriched subtype. ADVANCES IN KNOWLEDGE: Mammographic features can noninvasively visualize breast tumor phenotype characteristics.
[Keywords]: Mammography; Calcification; Spiculated mass; Infiltrating ductal carcinoma; Logistic regression

Introduction

Breast cancer is one of the most frequent malignancies worldwide with differing clinical outcomes[1]. The fact is that in America, 1 out of 8 women (12.4%) will be diagnosed with female breast cancer in their lifetime (https://seer.cancer.gov/)[2-3]. Gene expression analyses identify four major molecular subtypes unique subgroups (the St Gallen Consensus Conference, 2013)[2-5]. HER2-enriched subtype seem to benefit the most from dual HER2 blockade with lapatinib/trastuzumab or neoadjuvant trastuzumab, in combination with chemotherapy[5-6].

Radiogenomics analysis of breast cancer revealed connections between molecular subtypes and imaging phenotypes[7].The characterization of mammographic microcalcifications are valuable in cancer screening, preoperative evaluations of disease extent as well as surveillance after treatment[8-10].Among subtypes,

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HER2-subtype have been shown to have a higher incidence of calcifications[11]. To the best of our knowledge, little is known microcalcification-associated HER2-enriched breast cancer. Patients with HER2-enriched breast cancer were most likely to present with a non-spiculated mass on their mammograms[12].

HER2-enriched molecular subtype determines whether certain drugs and therapy methods are recommended[13-15]. A resent published meta-analysis[16] found that there were significant differences in locoregional recurrence between the HER2-enriched and luminal molecular subtype (OR 1.64) and the reduced risk in HER2-enriched compared with triple-negative molecular subtype breast cancers approached statistical significance (OR 0.75) [15, 17]. In some tumors, it is difficult to differentiate between IHC1+ and IHC2+ or between IHC2+ and IHC3+ HER2 expression scores. The Guideline also recommend that if results are equivocal, reflex testing should be performed using an alternative assay(IHC or FISH).Sometimes it is not feasible to acquire adequate tissue for analysis(especially IHC2+) before the initiation of treatment because of inoperability, small biopsy specimens, or sampling artifact. In this situation, our model will be helpful to decision-making. Therefore, we aim to explore associations between HER2-subtype and the mammographic features.

Methods

Patients

This is a retrospective study, and ethical approval was obtained. This analysis comprised an evaluation of the institutional database for medical records from 2012 to 2017 to identify patients with histologically confirmed breast cancer. Inclusion criteria:(a)infiltrating ductal carcinoma (b) mammographic imaging with intermediate-concern or malignant calcification (c)tumor size were available (d)histopathologic data (histologic grade (HG), the estrogen receptor (ER), HER-2 status; Ki-67 status, progesterone receptor (PR) status, and lymph node metastasis) were available.

Mammographic features evaluation

Two radiologists, who were blinded to the histological features assessed the MG images for this study, and a consensus was reached. By referring to previous studies[12, 17], patients with a mass on the mammogram were divided into groups of spiculated and non-spiculated depending on the margin status of the mass, respectively. Spiculated masses are defined as masses with lines radiating from their margins (Fig1).Lesions classified as non-spiculated were circumscribed, microlobulated, obscured or indistinct (Fig1). Based on TNM staging criteria, patients with a mass on the mammogram were divided into groups of $\leqslant$2cm (T1) and >2cm (T2 and T3)

By referring to previous studies[19 20],the calcification was visually analyzed according to the BI-RADS classification, the reading radiologist could choose multiple terms from the morphologic features (intermediate concern calcification=coarse heterogeneous or amorphous, malignant calcification= fine linear or fine pleomorphic),the distribution descriptors (intermediate concern calcification=clustered, malignant calcification=segmental or linear ductal).Other measurements (Fig2) of mammographic breast calcification, such as extension (> 2

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cm vs ⩽ 2 cm in extent), diameter (⩽ 0.5 mm vs > 0.5 mm) and density (⩽ 20/cm^2 vs > 20/cm^2 in density) were also recorded.

Pathology and breast cancer molecular subtype

Tumor pathology reports were reviewed, with a focus on the following histological parameters: HG, status of ER, PR and HER2.ER, PR, and Ki-67, lymph node status and lymphovascular invasion were evaluated[21]. In our study, HER2 status was defined by the 2013 Guidelines (American Society of Clinical Oncology) [22]. Four breast cancer molecular subtypes (Luminal A-subtype, Luminal B-subtype, HER2-enriched -subtype and basal-subtype) were grouped by IHC based on previous reports[6, 23]

Statistical analysis

The chi-square test (using SPSS software, version 15.0) was used to evaluate HER2-enriched molecular subtype status correlation with age and pathologic characteristics. In this study, a heat map served as a visual representation of trends between the HER2-subtype status and the mammographic features (Excel 2010, Microsoft Company). Differences between breast cancers with HER2-enriched molecular subtype and non-HER2-enriched molecular subtype were tested using the chi-square test, as well as univariate and multivariate binary logistic regression analyses. The ORs and corresponding 95% CIs were determined, also using SPSS. Discrimination was measured with the area under the receiver operating characteristic curve (AUC). P values of less than 0.05 were considered statistically significant.

Results

283 microcalcification-associated breast cancers were identified were 57 (20.1%) HER2-enriched, 59 (20.8%) Luminal A, 146 (51.6%) Luminal B and 21 (7.4%) basal subtypes. Luminal A-subtype, Luminal B-subtype and basal-subtype were grouped as non-HER2-enriched molecular subtype (N=226).Associations between clinicopathologic factors and HER2-enriched molecular subtype are presented in Table 1. HER2-enriched molecular subtype rates were significantly higher in grade 3 35 of 57 [61.4%]) than grade1+2 (75 of 225 [33.3%]).No significant associations were observed between clinicopathologic factors (age, lymphovascular invasion and lymph node status) and the HER2-subtype.

Hierarchical clustering (Figure 3) shown groups of HER2-enriched molecular subtype status and mammographic features. On univariate analysis, HER2-enriched molecular subtype rates were significantly higher (a) in tumor size<=2cm 33 of 57 [68.4%]) than in tumor size>2cm lesions (22 of 226 [9.7%]) (P =0.007), (b) in non-spiculated mass 39 of 57 [68.4%]) than in spiculated mass lesions (18 of 226 [7.9%]) (P =0.034)，(c) in calcifications extent >2 cm (41of 57[71.9%]) lesions than in calcifications extent<=2 cm lesions (16 of 226 [7.1%]) (P<0.001)and (d) in calcification density ＞20/cm^2 (44 of 57[71.2%]) lesions than in calcification density<=20/cm^2 lesions (13 of 226 [5.8%]) (P=0.034). Associations between mammographic features and HER2-enriched molecular subtype are presented in Table 2.

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On univariate logistic regression analysis, four mammographic features (tumor size>2cm vs. size⩽2 cm OR: 0.447 95% CI: 0.248 to 0.806, P=0.007, spiculated mass vs. non-spiculated mass OR: 0.263 95% CI: 0.141 to 0.489, P<0.001 and calcifications extent >2 cm vs. calcifications extent <=2 cm OR: 8.429, 95% CI: 3.575 to 19.875 P<0.001; calcification density ＞20/cm2 vs. calcification density⩽20cm2 OR: 2.178, 95% CI: 1.041 to 4.554 P=0.039) was significantly associated with HER2-enriched molecular subtype.

On multivariate logistic regression analysis, three mammographic features (tumor size>2cm vs. size⩽2 cm OR: 0.415 95% CI: 0.215 to 0.802, P=0.009, spiculated mass vs. non-spiculated mass OR: 0.226 95% CI: 0.114 to 0.446, P<0.001 and calcifications extent >2 cm vs. calcifications extent <=2 cm OR: 7.754, 95% CI: 3.100 to 19.339 P<0.001) were independent predictors. Our results indicated that small tumor size, non-spiculated mass and calcification extent >2 cm are more likely to be HER2 molecular subtype (AUC: 0.751 95%CI: 0.701 to 0.854).

Discussion

Recently, molecular characterization of breast cancer has led to a better understanding of the disease. The HER2-subtype, which meant a poor prognosis in landmark studies of cancer genomics, has significantly benefited from the era of anti-HER2 targeted therapies[24]. Review of previous records shown that female patients with HER2-positive breast cancer who received trastuzumab had significantly improved prognosis compared with female patients with HER2-negative breast cancer [25]. A series of pivotal trials showed the clinical benefit of trastuzumab-based therapy in combination with chemotherapy (adjuvant and neo-adjuvant) have led to a new standard of care for female patients with operable and metastatic HER2-positive disease[26-28]. In recent years, many study has focused on the development of MRI biomarkers for evaluation of the prognosis of breast cancer[29-32]. However, the proposed technique is not practical at lower field strengths (1.5 T or 3 T) to detect microcalcifications, and cost much more than mammography. HER2-enriched breast cancers have been found to have a higher incidence of calcifications[11].

Mammographic features can noninvasively visualize breast tumor phenotype characteristics[33]. Spiculation of breast malignant lesions is frequently the result of significant desmoplastic reaction[34]. Spiculation is a characteristic appearance of invasive breast carcinoma at mammography as well as a useful criterion in the clinical diagnosis of the disease[12]. Several investigators recently reported that masses with a spiculated margin were significantly more often in patients with the luminal A-subtype than in those with other subtypes[12]. The status of Ki67 and HER2 may perhaps be the most significant factors affecting the visualization of a spiculated mass. However, questions regarding the most significant contributing factor affecting the absence or presence of a spiculated mass remain unanswered.

Many studies have reported that mammographic microcalcifications as an associated finding of mass were more frequent in HER2-enriched molecular subtype than non-HER2-enriched molecular subtype. Seo et al [35] and coworkers demonstrated that microcalcifications were more significantly frequent in carcinomas with

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HER2-subtype (56%) than in those without HER2-subtype (40%). Cen et al[36] found that calcification >2 cm in extent can predict HER2 subtype. Patel[37] and coworkers indicated that patients with malignant lesions that overexpressed HER2 were more likely to have pleomorphic and heterogeneous calcifications. Actually, they did not perform comprehensively assess the appearance of the breast cancer HER2-enriched molecular subtype. We demonstrated that small tumor size, non-spiculated mass and calcification extent >2 cm are more likely to be HER2 molecular subtype. The model demonstrated high prediction accuracy for predicting HER2 subtype, with an AUC of 0.759.

Our study has limitations. Firstly, invasive lobular carcinomas is not included in this study. It is appreciated that the majority of invasive lobular carcinomas lack HER2 overexpression cases of invasive lobular carcinomas with HER2 amplification or overexpression typically represent the pleomorphic variant. Secondly, microcalcifications combined with mass are not an obligate finding associated to IDC, so our speculations could be applied only to a part of the cancers. However, HER2-positive breast cancer is characteristically a mass with microcalcifications, we therefore believe our findings are not significantly influence by such factors. Thirdly, this was a retrospective study and only single-center data were collected. And the predictive value of the mammographic features is modest.

In conclusion, this study presents a prediction model that incorporates the mammographic features of tumor size, non-spiculated mass and calcification extent, which can potentially be used to preoperative predict breast cancer HER2-enriched subtype. Our results indicated that small tumor size, non-spiculated mass and calcification extent>2 cm are more likely to be HER2 molecular subtype. And the predictive model showed a good discrimination.

References

[1] Royston P, Altman DG: External validation of a Cox prognostic model: principles and methods. BMC medical research methodology 2013, 13:33.

[2] Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thurlimann B, Senn HJ, Panel m: Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Annals of oncology : official journal of the European Society for Medical Oncology 2013, 24:2206-23.

[3] Harbeck N, Thomssen C, Gnant M: St. Gallen 2013: brief preliminary summary of the consensus discussion. Breast care 2013, 8:102-9.

[4] Boisserie-Lacroix M, Hurtevent-Labrot G, Ferron S, Lippa N, Bonnefoi H, Mac Grogan G: Correlation between imaging and molecular classification of breast cancers. Diagnostic and interventional imaging 2013, 94:1069-80.

[5] Prat A, Cheang MC, Galvan P, Nuciforo P, Pare L, Adamo B, Munoz M, Viladot M, Press MF, Gagnon R, Ellis C, Johnston S: Prognostic Value of Intrinsic Subtypes in Hormone Receptor-Positive Metastatic Breast Cancer Treated With Letrozole With or Without Lapatinib. JAMA oncology 2016, 2:1287-94.

[6] Prat A, Pineda E, Adamo B, Galvan P, Fernandez A, Gaba L, Diez M, Viladot M,

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Arance A, Munoz M: Clinical implications of the intrinsic molecular subtypes of breast cancer. Breast 2015, 24 Suppl 2:S26-35.
[7] An YY, Kim SH, Kang BJ, Park CS, Jung NY, Kim JY: Breast cancer in very young women (<30 years): Correlation of imaging features with clinicopathological features and immunohistochemical subtypes. European journal of radiology 2015, 84:1894-902.
[8] Weigel S, Decker T, Korsching E, Hungermann D, Bocker W, Heindel W: Calcifications in digital mammographic screening: improvement of early detection of invasive breast cancers? Radiology 2010, 255:738-45.
[9] Bae MS, Moon WK, Chang JM, Cho N, Park SY, Won JK, Jeon YK, Moon HG, Han W, Park IA: Mammographic features of calcifications in DCIS: correlation with oestrogen receptor and human epidermal growth factor receptor 2 status. European radiology 2013, 23:2072-8.
[10] Antonio AL, Crespi CM: Predictors of interobserver agreement in breast imaging using the Breast Imaging Reporting and Data System. Breast cancer research and treatment 2010, 120:539-46.
[11] Cho N: Molecular subtypes and imaging phenotypes of breast cancer. Ultrasonography 2016, 35:281-8.
[12] Liu S, Wu XD, Xu WJ, Lin Q, Liu XJ, Li Y: Is There a Correlation between the Presence of a Spiculated Mass on Mammogram and Luminal A Subtype Breast Cancer? Korean journal of radiology 2016, 17:846-52.
[13] Untch M, Harbeck N, Huober J, von Minckwitz G, Gerber B, Kreipe HH, Liedtke C, Marschner N, Mobus V, Scheithauer H, Schneeweiss A, Thomssen C, Jackisch C, Beckmann MW, Blohmer JU, Costa SD, Decker T, Diel I, Fasching PA, Fehm T, Janni W, Luck HJ, Maass N, Scharl A, Loibl S: Primary Therapy of Patients with Early Breast Cancer: Evidence, Controversies, Consensus: Opinions of German Specialists to the 14th St. Gallen International Breast Cancer Conference 2015 (Vienna 2015). Geburtshilfe und Frauenheilkunde 2015, 75:556-65.
[14] Jackisch C, Harbeck N, Huober J, von Minckwitz G, Gerber B, Kreipe HH, Liedtke C, Marschner N, Mobus V, Scheithauer H, Schneeweiss A, Thomssen C, Loibl S, Beckmann MW, Blohmer JU, Costa SD, Decker T, Diel I, Fasching PA, Fehm T, Janni W, Luck HJ, Maass N, Scharl A, Untch M: 14th St. Gallen International Breast Cancer Conference 2015: Evidence, Controversies, Consensus - Primary Therapy of Early Breast Cancer: Opinions Expressed by German Experts. Breast care 2015, 10:211-9.
[15] Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, Thurlimann B, Senn HJ, Panel M: Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Annals of oncology : official journal of the European Society for Medical Oncology 2015, 26:1533-46.
[16] McGuire A, Lowery AJ, Kell MR, Kerin MJ, Sweeney KJ: Locoregional Recurrence Following Breast Cancer Surgery in the Trastuzumab Era: A Systematic Review by Subtype. Annals of surgical oncology 2017, 24:3124-32.
[17] Gao B, Zhang H, Zhang SD, Cheng XY, Zheng SM, Sun YH, Zhang DW, Jiang Y,

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Tian JW: Mammographic and clinicopathological features of triple-negative breast cancer. The British journal of radiology 2014, 87:20130496.
[18] Houvenaeghel G, Goncalves A, Classe JM, Garbay JR, Giard S, Charytensky H, Cohen M, Belichard C, Faure C, Uzan S, Hudry D, Azuar P, Villet R, Gimbergues P, Tunon de Lara C, Martino M, Lambaudie E, Coutant C, Dravet F, Chauvet MP, Chereau Ewald E, Penault-Llorca F, Esterni B: Characteristics and clinical outcome of T1 breast cancer: a multicenter retrospective cohort study. Annals of oncology : official journal of the European Society for Medical Oncology 2014, 25:623-8.
[19] Li JJ, Chen C, Gu Y, Di G, Wu J, Liu G, Shao Z: The role of mammographic calcification in the neoadjuvant therapy of breast cancer imaging evaluation. PloS one 2014, 9:e88853.
[20] Cen D, Xu L, Zhang S, Zhou S, Huang Y, Chen Z, Li N, Wang Y, Wang Q: BI-RADS 3-5 microcalcifications: prediction of lymph node metastasis of breast cancer. Oncotarget 2017, 8:30190-8.
[21] Shah MV, Wiktor AE, Meyer RG, Tenner KS, Ballman KV, Green SJ, Sukov WR, Ketterling RP, Perez EA, Jenkins RB: Change in Pattern of HER2 Fluorescent in Situ Hybridization (FISH) Results in Breast Cancers Submitted for FISH Testing: Experience of a Reference Laboratory Using US Food and Drug Administration Criteria and American Society of Clinical Oncology and College of American Pathologists Guidelines. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2016, 34:3502-10.
[22] Zhang H, Zhang S, Wang Y, Li D, Xu L, Liu Q, Duan X, Liu Y, Li T: [Re-evaluation of HER2 status in 1 501 invasive breast cancers according to the 2013 American Society of Clinical Oncology/College of American Pathology guidelines]. Zhonghua bing li xue za zhi = Chinese journal of pathology 2015, 44:42-7.
[23] Dieci MV, Orvieto E, Dominici M, Conte P, Guarneri V: Rare breast cancer subtypes: histological, molecular, and clinical peculiarities. The oncologist 2014, 19:805-13.
[24] Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lonning PE, Borresen-Dale AL, Brown PO, Botstein D: Molecular portraits of human breast tumours. Nature 2000, 406:747-52.
[25] Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH: Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010, 28:92-8.
[26] Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. The New England journal of medicine 2005, 353:1673-84.
[27] Baselga J, Perez EA, Pienkowski T, Bell R: Adjuvant trastuzumab: a milestone in the treatment of HER-2-positive early breast cancer. The oncologist 2006, 11 Suppl

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1:4-12.
[28] Vici P, Viola G, Botti C, Rossi S, Vitucci C, Corsetti S, Di Lauro L, Sergi D, Foggi P, Perri P, Tirelli C, Mottolese M, Fattoruso SI, Lopez M: Docetaxel in the adjuvant therapy of HER-2 positive breast cancer patients. La Clinica terapeutica 2008, 159:449-52.
[29] Trop I, LeBlanc SM, David J, Lalonde L, Tran-Thanh D, Labelle M, El Khoury MM: Molecular classification of infiltrating breast cancer: toward personalized therapy. Radiographics : a review publication of the Radiological Society of North America, Inc 2014, 34:1178-95.
[30] Uematsu T, Kasami M, Watanabe J: Is evaluation of the presence of prepectoral edema on T2-weighted with fat-suppression 3 T breast MRI a simple and readily available noninvasive technique for estimation of prognosis in patients with breast cancer? Breast cancer 2014, 21:684-92.
[31] Alili C, Pages E, Curros Doyon F, Perrochia H, Millet I, Taourel P: Correlation between MR imaging - prognosis factors and molecular classification of breast cancers. Diagnostic and interventional imaging 2014, 95:235-42.
[32] Thomassin-Naggara I, Trop I, Lalonde L, David J, Peloquin L, Chopier J: Tips and techniques in breast MRI. Diagnostic and interventional imaging 2012, 93:828-39.
[33] Gutman DA, Dunn WD, Jr., Grossmann P, Cooper LA, Holder CA, Ligon KL, Alexander BM, Aerts HJ: Somatic mutations associated with MRI-derived volumetric features in glioblastoma. Neuroradiology 2015, 57:1227-37.
[34] Gokalp G, Topal U, Yildirim N, Tolunay S: Malignant spiculated breast masses: dynamic contrast enhanced MR (DCE-MR) imaging enhancement characteristics and histopathological correlation. European journal of radiology 2012, 81:203-8.
[35] Seo BK, Pisano ED, Kuzimak CM, Koomen M, Pavic D, Lee Y, Cole EB, Lee J: Correlation of HER-2/neu overexpression with mammography and age distribution in primary breast carcinomas. Academic radiology 2006, 13:1211-8.
[36] Cen D, Xu L, Li N, Chen Z, Wang L, Zhou S, Xu B, Liu CL, Liu Z, Luo T: BI-RADS 3-5 microcalcifications can preoperatively predict breast cancer HER2 and Luminal a molecular subtype. Oncotarget 2017, 8:13855-62.
[37] Patel TA, Puppala M, Ogunti RO, Ensor JE, He T, Shewale JB, Ankerst DP, Kaklamani VG, Rodriguez AA, Wong ST, Chang JC: Correlating mammographic and pathologic findings in clinical decision support using natural language processing and data mining methods. Cancer 2017, 123:114-21.

Figures Legends

Figure 1: Invasive carcinomas associated with microcalcification (Fig 1A tumor size>2 cm vs. Fig 1B tumor size ⩽2cm Fig 1A non-spiculated mass vs. Fig 1B spiculated mass)

Figure 2: Measurements of mammographic breast calcification (extent, diameter and density)

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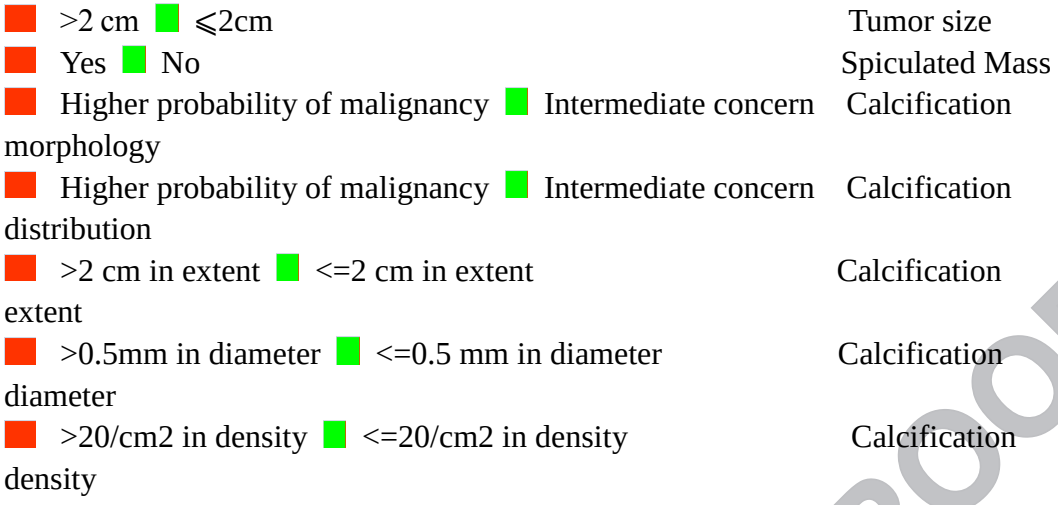

Figure 3: Clustering of samples of microcalcification-associated breast cancer HER2-enriched molecular subtype and non-HER2-enriched molecular subtype (n=283).

Figure 4: The model was developed with the tumor size, spiculated mass and calcification extent.And the discrimination of this model, as quantified by the AUC, was 0.759.

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Figure1

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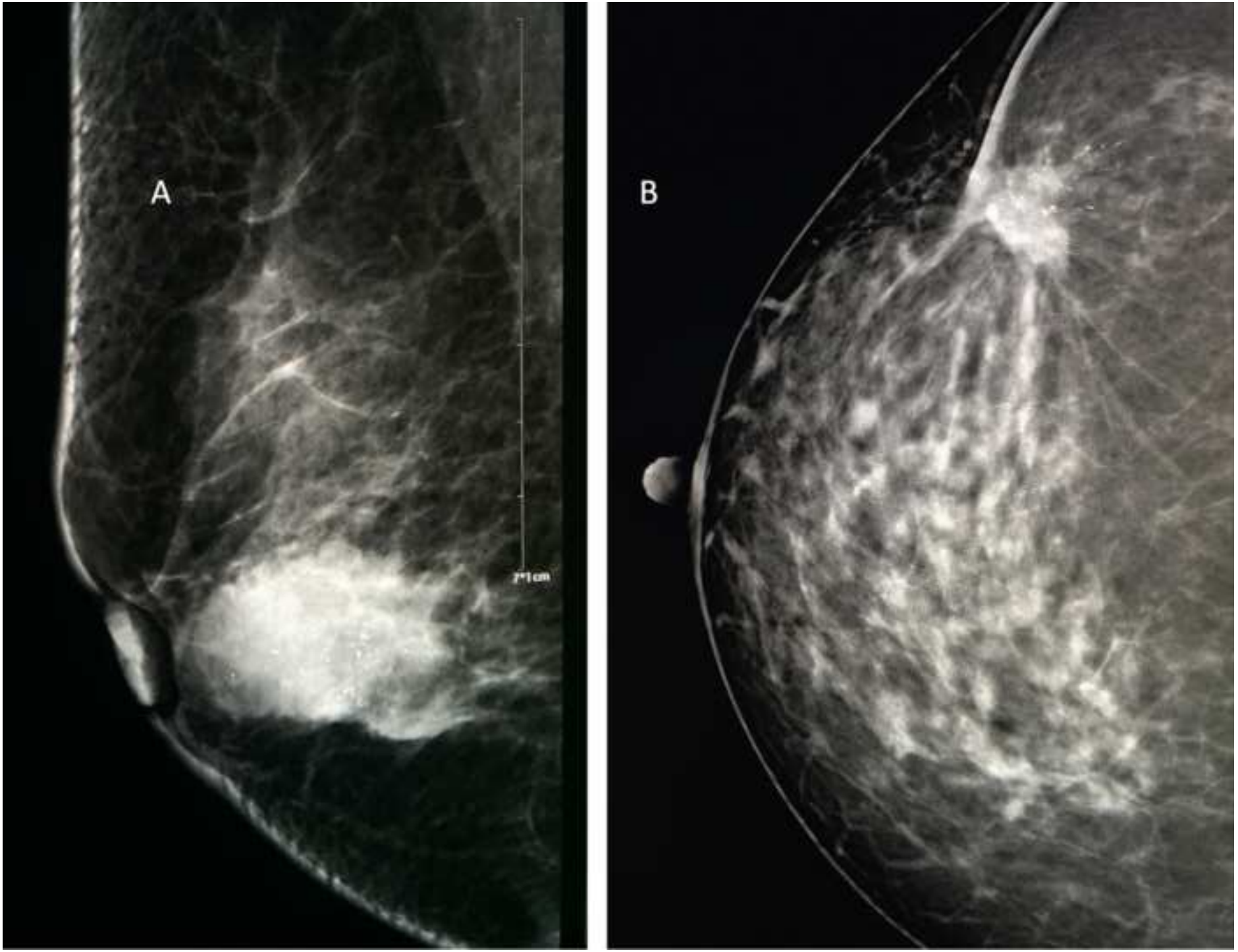

Figure2

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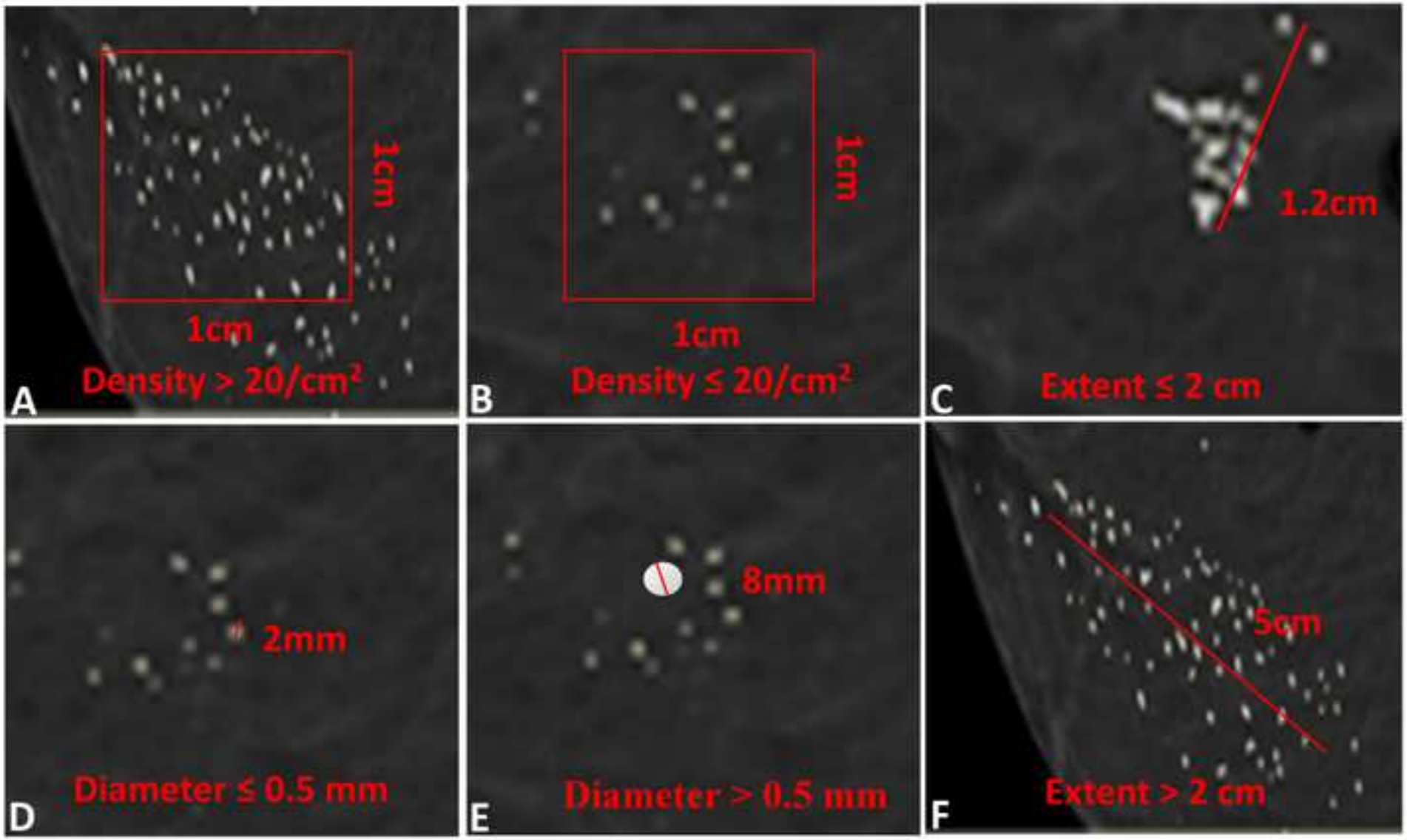

Figure3 Click here to download Figure Fig3.tif

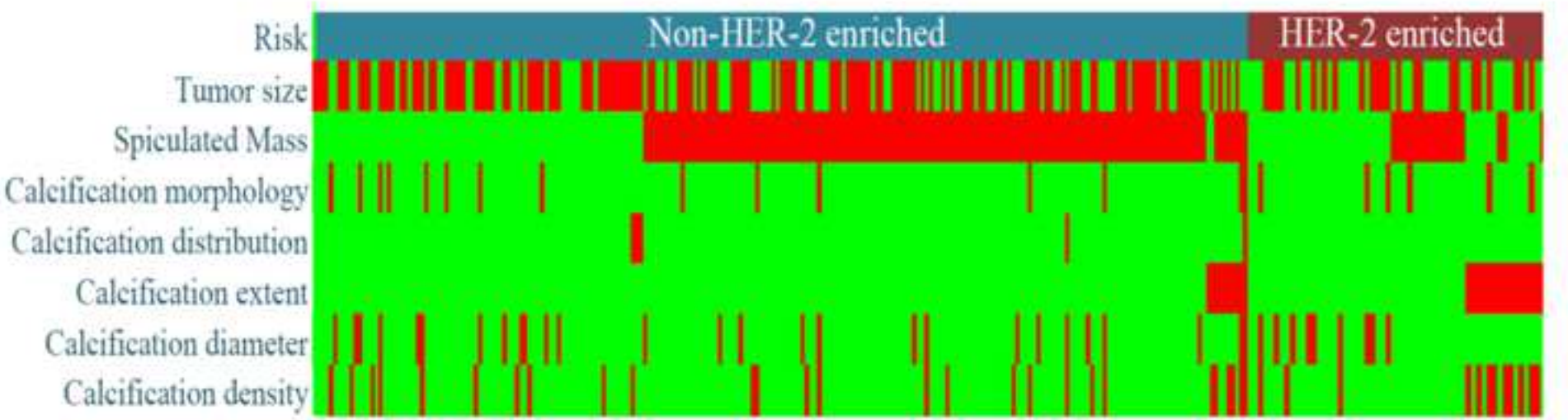

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Figure4

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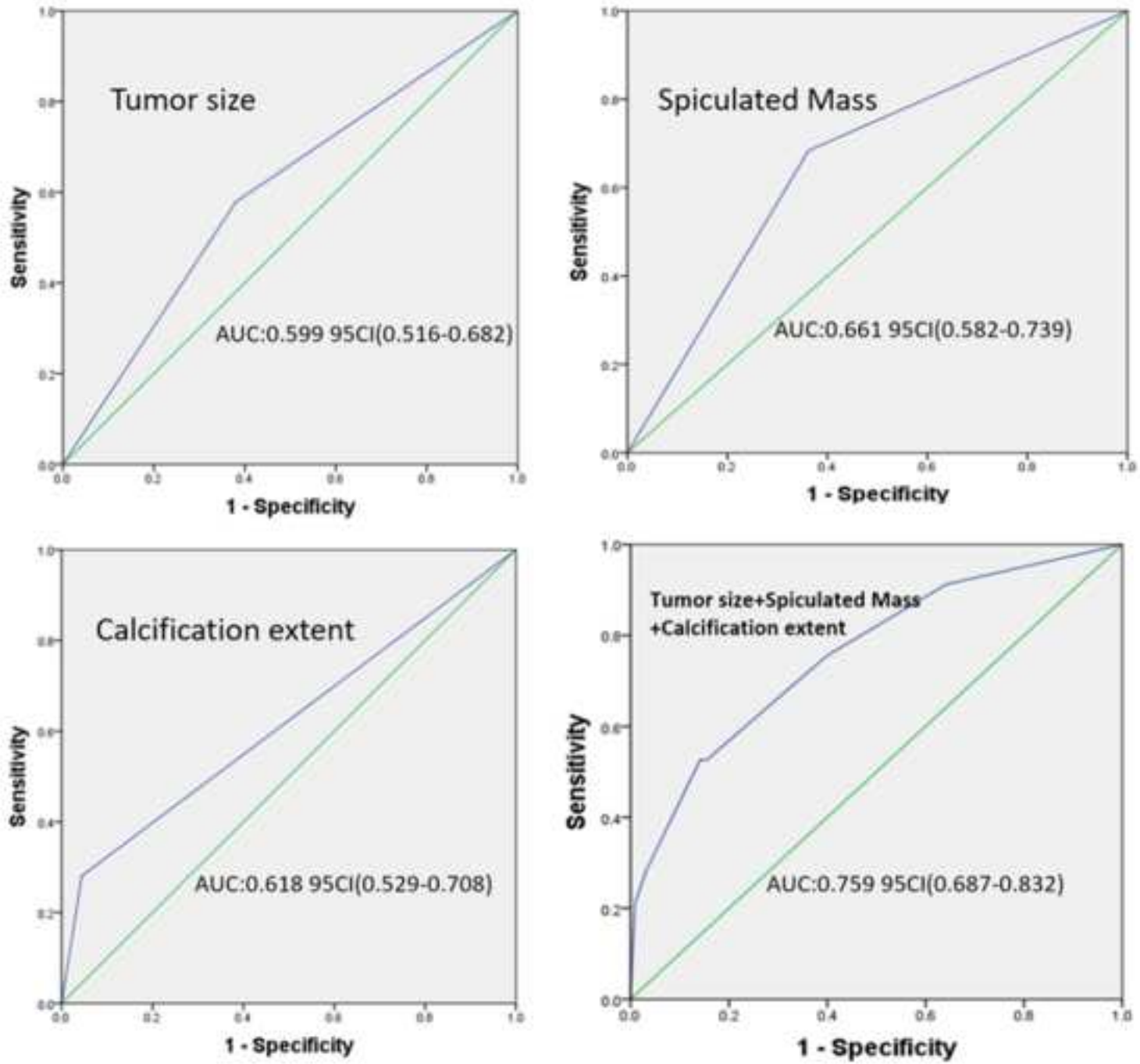

Table1 the tumor characteristics of HER-2 enriched subtype

	Non-HER-2 enriched	HER-2 enriched	χ^2	*P* value
Age			0.573	0.751
<35	13(5.8)	2(3.5)		
35-69	203(88.8)	53(93.0)		
≥70	10(4.4)	2(3.5)		
Recoded according to prevalence			0.094	0.759
<70	216(95.6)	55(96.5)		
≥70	10(4.4)	2(3.5)		
Grade			16.091	<**0.001**
G1	19(8.4)	1(1.8)		
G2	132(58.4)	21(36.8)		
G3	75(33.2)	35(61.4)		
Recoded according to prevalence			15.524	<**0.001**
G1-2	151(66.8)	22(38.6)		
G3	75(77.6)	35(45.9)		
Lymphovascular invasion			2.991	0.084
Negative	159(70.4)	36(63.2)		
Positive	67(29.6)	21(36.8)		
LN			0.036	0.851
Negative	130(57.5)	32(56.1)		
Positive	96(42.5)	25(43.9)		

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Table2 comparison of mammographic features between HER-2 enriched and Non-HER-2 enriched subtype

		Non-HER-2 enriched	HER-2 enriched	χ^2	*P value*
Tumor size				7.354	**0.007**
	⩽2 cm	86(38.1)	33(57.9)		
	>2cm	140(61.9)	24(42.1)		
Spiculated Mass				19.209	**<0.001**
	No	82(36.3)	39(68.4)		
	Yes	144(63.7)	18(31.6)		
Calcification morphology,No (%)				1.002	0.317
	Intermediate concern	211(93.4)	51(89.5)		
	Higher probability of malignancy	15(6.6)	6(10.5)		
Calcification distribution,No (%)				1.284	0.257
	Intermediate concern	221(97.8)	57(100)		
	Higher probability of malignancy	5(2.2)	0(0)		
Calcification extent,No (%)				30.504	**<0.001**
	<=2 cm in extent	216(95.6)	41(71.9)		
	>2 cm in extent	10(4.4)	16(28.1)		
Calcification diameter ,No (%)				0.605	0.437
	<=0.5 mm in diameter	199(88.1)	48(84.2)		

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	>0.5mm in diameter	27(11.9)	9(15.8)		
Calcification density,No (%)				4.501	**0.034**
	<=20/cm^2 in density	199(88.1)	44(77.2)		
	>20/cm^2 in density	27(11.9)	13(22.8)		

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Table 3

Table3 binary logistic regression analysis of prognostic factors for HER2-enriched subtype

	β	Wald	Sig.	OR	95.0% CI for OR	
					Lower	Upper
Tumor size	-0.879	6.841	0.009	0.415	0.215	0.802
Spiculated Mass	-1.489	18.366	0	0.226	0.114	0.446
Calcification extent	2.048	19.168	0	7.754	3.1	19.399
Constant	-0.491	2.947	0.086	0.612		

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